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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/768,350	HE ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3 and 5-8* is/are rejected.

7)☒ Claim(s) *1 and 2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant filed a response to the Non-Final Rejection of April 20, 2005 on July 6, 2005 and also submitted a supplemental response August 29, 2005. Applicant has indicated that the supplemental response of August 29, 2005 has incorporated the response filed July 6, 2005. In the claims submitted August 29, 2005, claims 4, 9-11 are cancelled. Claims 1-3, 5-8 are amended.

Claims 1-3, 5-8 are currently under consideration.

Claim Objection

Claims 1 and 2 are objected to as the matters regarding the deposit of these biological materials are incomplete.

It is noted that in the Response by the Applicant, January 18, 2005, page 5, that the Applicant has deposited IC1 and IAC1 with American Type Culture Collection in Manassas, VA and that a copy of the Budapest Treaty Deposit Form was enclosed with the Response. The Applicant has indicated that a copy of the Certificate of Deposit and Viability would be submitted; however, no copy has been received. Further, there is no indication as to public availability. If the deposit is made under the Budapest treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific biological materials have been deposited under the Budapest Treaty and that the biological materials will be irrevocably and without restriction or condition released to the public upon issuance of a patent would satisfy the deposit requirement made herein. If the

deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 after the last request or for the effective life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit will be made (see 37 CFR 1.807); and

(e) the deposit will be replaced if it should ever become inviable.

Applicant's attention is directed to MPEP §2400 in general, and specifically to §2411.05, as well as to 37 CFR § 1.809(d), wherein it is set forth that "the specification shall contain the accession number for the deposit, the date of the deposit, and a description of the deposited material sufficient to specifically identify it and to permit examination." The specification should be amended to include this information, however, Applicant is cautioned to avoid the entry of new matter into the specification by adding any other information.

Withdrawn Rejections

35 U.S.C. § 112, first parag.

Applicant's arguments, see page 5 of Applicant's response, filed August 29, 2005, with respect to the rejection of claims 1 and 2 have been fully considered and are persuasive. Applicant has amended the claims. The rejection of claims 1 and 2 has been withdrawn.

35 U.S.C. § 112, second parag.

Applicant's arguments, see page 5 of Applicant's response, filed August 29, 2005, with respect to the rejection of claims 1, 2, 3, 6 have been fully considered and are persuasive. Applicant has amended the claims. The rejection of claims 1, 2, 4, 6 has been withdrawn.

35 U.S.C.§ 103(a)

Applicant's arguments, see page 6 of Applicant's response, filed August 29, 2005, with respect to the rejection of claims 3-8 under 35 U.S.C § 103(a) have been fully considered and are persuasive. Applicant has provided a Declaration by Dr. He and have amended the claims. The rejection of claims 3-8 has been withdrawn.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 5-8 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

1) a method of introducing an IC1 ES cell into a C57BL/6 blastocyst, wherein said method comprises: introducing a transgene construct into IC1, wherein the transgene construct is stably integrated in the genome, injecting IC1 comprising the transgene construct into a C57BL/6 blastocyst, wherein said blastocyst is transplanted into a pseudopreganant mouse, and allowing said blastocyst to develop into a chimeric transgenic mouse,

2) a method of introducing an IAC1 ES cell into a C57BL/6 blastocyst, wherein said method comprises: introducing a transgene construct into IAC1, wherein the transgene construct is stably integrated in the genome, injecting IAC1 comprising the transgene construct into a C57BL/6 blastocyst, wherein said blastocyst is transplanted into a pseudopregnant mouse, and allowing said blastocyst to develop into a chimeric transgenic mouse, and

does not reasonably provide enablement for

1) a method of generating any transgenic C57BL/6 mouse and

2) a method of introducing any albino C57BL/6 ES cell into a C57BL/6 blastocyst. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claimed invention encompasses any method of generating a transgenic C57BL/6 mouse for producing genetically modified mice (in particular, see claim 3). At the time of filing, the art teaches that making transgenic mice is unpredictable. With regards to making overexpression mice, the art teaches that transgene constructs are unpredictable. An art example demonstrating the unpredictability in making transgenic animals is demonstrated by Hammer et al. 1990, Cell, 6: 1099-1112. Hammer et al. created both transgenic mice and rats expressing the human HLA-b27 gene and beta-2

microglobulin. Although both transgenic animals bearing the HLA-b27 gene expressed the gene, transgenic mice did not show any HLA-b27 associated disease, whereas the transgenic rats demonstrated most of the HLA-b27 related diseases (Hammer, et al., page 1099, col. 2, lines 20-28). This shows that the integration of a transgene into an alternative species may result in widely different phenotype responses even in animals of the same species. Additionally, promoters and enhancer elements may not function in all the species because they may require specific cellular factors. For example, Cowan et al. 2003, Xenotransplantation, 10: 223-231 teach that promoters of three human genes, ICAM-2, hCRPs, and PECAM-1, which are predominantly expressed in vascular endothelium in mice and pigs. When tissue specific expression was measured, it was found that while mice showed a distinct expression profile of the three human genes, the tissue expression profiles of the three human gene promoters were distinctly different in pigs. The authors concluded that "promoter performance in mice and pigs was not equivalent," and that "the weak expression driven by the human ICAM-2 promoter in pigs relative to mice suggests the need for additional regulatory elements to achieve species-specific gene expression in pigs. In addition to this, the transgene product may not have the same activity in the original animal. Hammer et al. 1986, J. of Anim. Sci., 63: 269-278 teach that while transgenic mice that overexpressed human growth hormone exhibited enhanced growth, transgenic pigs that expressed human growth hormone did not increase weight gain (Hammer et al., page 276, under "Effect of Foreign GH on Growth"). As these issues relate to the instant invention an artisan cannot reasonably predict that any promoter and any heterologous gene, and

thus, any transgene construct has any activity and thus any phenotype, in the transgenic overexpression animal. While the specification teaches that ES cells lines, IC1 and IC2, from black C57BL/6 mice were electroporated by two different constructs containing a neo gene cassette, wherein the first construct, the neo cassette was inserted into a partially cloned p53 gene and wherein the second construct, the neo gene cassette was linked to a GFP gene (specification, page 18), the specification does not provide any guidance to overcome the hurdles of transgenesis, as described above. As such, making transgene constructs and transgenic mice is undue experimentation because each transgene construct would need to be empirically determined. Thus, for the reasons described above, the claimed invention is not enabled any transgenic C57BL/6 overexpression mouse.

The claimed invention also encompasses transgenic knockout C57BL/6 mice. At the time of filing, the art teaches unpredictability in generating knockout mice. The art teaches that there is unpredictability in obtaining any knockout mouse because the phenotype exhibited by the mouse is unpredictable. For example, the art teaches that gene targeting of the endothelin loci subsequently led to the creation of mice with Hirschsprung's disease (aganglionic megacolon) instead of the anticipated phenotype (abnormal control of blood pressure)(Moreadith and Radford, 1997, J. Mol. Med., 75: 208-216, page 208, 2nd col., 2nd parag.). Another reason for the unpredictability in generating knockout mice is that their phenotype may not necessarily be the result of the gene disruption. The art teaches that while the promise of gene targeting had been to reveal the *in vivo* function of a gene of interest, the functional relevance of gene

targeting has been questioned because the mutation might lead to an avalanche of compensatory processes (up- or downregulation of gene products) and resulting secondary phenotypical changes. Thus, a null mutant organism might not only lack the produce of a single gene, but might also possess a number of developmental, physiological, or even behavioral process that have been altered to compensate for the effect of the null mutation (Gerlai, 1996, Trends Neurosci, 19: 177-181, page 177, 1st col., 1st parag.). Gerlai teaches an example wherein background genotype can confound the exhibited phenotypes. Targeted disruption of a gene of interest, α, might lead to changes in expression of alleles b and B for gene β. A regulatory change in gene β might lead to different phenotypic changes, depending on which allele (b or B) is present in the organism with the null mutation in gene α. The upshot of this problem is that due to this polymorphism in the genetic background, one cannot conclude for certain that a phenotypic change exhibited in a null-mutant mouse resulted from the null mutation or to the genetic background (Gerlai, page 177, 1st col., under "Polymorphism in the genetic background might make the results of gene-targeting studies difficult to interpret"). As these issues relate to the instant invention, while the specification teaches that a transgene construct was introduced to two ES cell lines (specification, page 18) and indicates that Southern hybridization analysis could be used to detect a transgene construct (specification, page 17), the specification does not indicate how to predictably obtain any knockout mouse, wherein the artisan would reliably know the biological relationship between the phenotypes exhibited by the mice and the disrupted

gene. For this reason, specification does not enable an artisan to practice the claimed invention for its full breadth of any knockout C57BL/6 mouse.

With regards to the broad scope of any albino C57BL/6 ES cell (e.g. see claim 5), the specification teaches that an ES cell line, IAC1, was made from an albino C57BL/6-Tyr^{c-2J} mouse. While the specification teaches that one cell was made and indicates that another albino strain (C57BL/10snJTyrC-11J, see specification, page 20) was used to generate another albino C57BL ES cell, the examples of 2 kinds of ES cells does not enable an artisan to make and use any albino C57BL ES cell for its fullest breadth. The Applicant teaches that embryos were obtained by flushing the uterus of C57BL/6 and C57BL/6J-Tyr $^{c-2J}$ mice 5 days after natural mating, that the embryos were transferred to plates comprising gamma-irradiated mouse embryonic fibroblasts and ES medium (which contained 15% FBS, 1mM non-essential amino acids, 0.1mM 2-mercaptoethanol, and 1000 units/ml LIF) (specification, page 18). One of the ES cell lines obtained from C57BL/6 black mice using this method was IC1. The Applicant indicates that when IC1 cells were injected into albino C57BL/6J-Tyr $^{c-2J}$ blastocysts, that 15.2% of the mice that were obtained were chimeras and that 1 of 15 of the transgenic projects using these ES cells and blastocyst combinations results in germline transmission. While the Applicant provides this teaching, the art teaches that other methods can be used to generate ES cells and that the ES cells that are obtained by other methods do not behave like the ES cells taught in the specification. For example, Schuster-Gossler et al. 2001, Biotechniques, 31: 1022-1026 teach that ES cells obtained from C57BL/6 mice were obtained by culturing blastocysts in a droplet of

KSOM media and then placing the blastocysts into plates containing mitomycin-C-treated mouse embryonic fibroblast cells and ES cell culture (which contains DMEM supplemented with 15% FBS, 2mM glutamine, 1mM nonessential amino acids, 1mM sodium pyruvate, 0.1mM β-mercaptoethanol, 10ng/ml of recombinant LIF, and an antibiotic mixture (Schuster-Gossler, et al, page 1022, 2nd col. under "B6 ES Cell Derivation and Culture"). Schulster-Gossler et al. teach that ES cells obtained from black C57BL/6 mice injected into albino C57BL/6J-Tyr $^{c-2J}$ blastocysts result in about 16.8% medium-to-high chimeras (obtained by averaging the numbers shown in Table 2 of Schuster-Gossler) and of which, most of the chimeric mice demonstrated germline transmission to progeny (Schuster-Gossler, et al., Table 2). The difference in number of chimeric mice which transmit to their germline (Applicant versus Schuster-Gossler, et al.) indicates that different ways in which ES cells are obtained contribute to differences in obtaining chimeric mice which transmit to the germline. With regards to what parts of the method of making ES cells contribute to this difference, neither the art nor the specification provide any guidance. That said, because there are these differences and the specification only teaches that specific cell lines were obtained using a specific method, an artisan cannot reasonably predict all the methods that can be used to generate all the different kinds of ES cells that can be obtained from albino C57BL/6J-Tyr $^{c-2J}$ blastocysts. Thus, for this reason, the scope of the claim is limited to IAC1.

In view of the lack of guidance, working examples, breadth of the claims, and state of the art of transgenesis at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

Examiner's note: While the Applicant has made a distinction of coat color to practice the claimed invention, nothing in the art indicates that difference in coat color amongst the same strain or substrain of mice would raise issues of enablement.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 5, 6, 7 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 uses the phrase, "C57 mice." However, there is no antecedent basis for "C57 mice." Claim 3 is also confusing because claim 3 is a method claim and line 3 of claim 3 is drawn to a mouse. Claim 3, step a) is also confusing because the transgene construct which is integrated in the genome of ES cells is also integrated in blastocysts. It is unclear how the blastocysts obtain the transgene construct when it is stably integrated in the ES cells. Claims 6 and 7 depend on claim 3.

Claim 5, step c) uses the phrase, "allowing said blastocyst to develop into chimeric transgenic mouse...". It appears this is a typographical error and that "a" is missing between "into" and "chimeric."

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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JH

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